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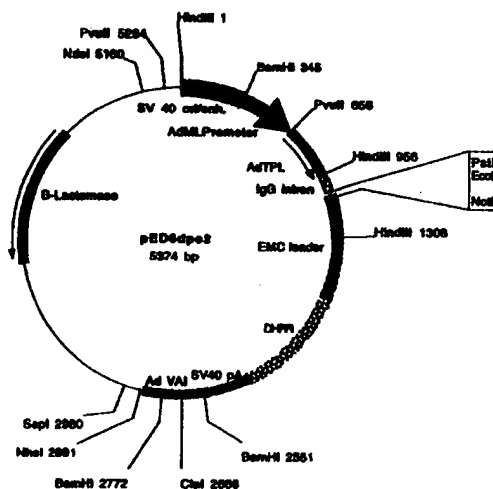
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**(54) Title:** SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

**(57) Abstract**

Novel polynucleotides and the proteins encoded thereby are disclosed.

1, 2, 4



Plasmid name: pED6dpc2  
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), MAR 19: 4485-4490.

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## SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of application Ser. No. 08/726,237, filed October 4, 1996.

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### FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

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### BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques  
30 clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader  
35 sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the  
40 polynucleotides encoding them that the present invention is directed.

### SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 282 to nucleotide 565;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 342 to nucleotide 565;
- 10 (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AX65\_22 deposited under accession number ATCC 98196;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AX65\_22 deposited under accession number ATCC 98196;
- 15 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX65\_22 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX65\_22 deposited under accession number ATCC 98196;
- 20 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of
- 25 (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

30 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 282 to nucleotide 565; the nucleotide sequence of SEQ ID NO:1 from nucleotide 342 to nucleotide 565; the nucleotide sequence of the full length protein coding sequence of clone AX65\_22 deposited under accession number ATCC 98196; or the nucleotide sequence of the mature protein coding sequence of clone AX65\_22 deposited



under accession number ATCC 98196. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AX65\_22 deposited under accession number ATCC 98196.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1 or SEQ ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:2;
- 10 (b) fragments of the amino acid sequence of SEQ ID NO:2; and
- (c) the amino acid sequence encoded by the cDNA insert of clone AX65\_22 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2.

15 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:56;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:56 from nucleotide 192 to nucleotide 2318;
- 20 (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BD335\_14 deposited under accession number ATCC 98196;
- (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BD335\_14 deposited under accession number ATCC 98196;
- 25 (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BD335\_14 deposited under accession number ATCC 98196;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BD335\_14 deposited under accession number ATCC 98196;
- 30 (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:57;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:57 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

5 (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:56 from nucleotide 192 to nucleotide 2318; the nucleotide sequence of the full-length protein coding sequence of clone BD335\_14 deposited under accession number ATCC 10 98196; or the nucleotide sequence of the mature protein coding sequence of clone BD335\_14 deposited under accession number ATCC 98196. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BD335\_14 deposited under accession number ATCC 98196. In yet other preferred embodiments, the present invention provides a polynucleotide 15 encoding a protein comprising the amino acid sequence of SEQ ID NO:57 from amino acid 148 to amino acid 240.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:56.

In other embodiments, the present invention provides a composition comprising 20 a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:57;

(b) the amino acid sequence of SEQ ID NO:57 from amino acid 148 to amino acid 240;

25 (c) fragments of the amino acid sequence of SEQ ID NO:57; and

(d) the amino acid sequence encoded by the cDNA insert of clone BD335\_14 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:57 or the amino acid sequence 30 of SEQ ID NO:57 from amino acid 148 to amino acid 240.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 206 to nucleotide 391;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BG241\_1 deposited under accession number ATCC 98196;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BG241\_1 deposited under accession number ATCC 98196;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG241\_1 deposited under accession number ATCC 98196;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG241\_1 deposited under accession number ATCC 98196;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 206 to nucleotide 391; the nucleotide sequence of the full length protein coding sequence of clone BG241\_1 deposited under accession number ATCC 98196; or the nucleotide sequence of the mature protein coding sequence of clone BG241\_1 deposited under accession number ATCC 98196. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BG241\_1 deposited under accession number ATCC 98196.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9, SEQ ID NO:8 or SEQ ID NO:11.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone BG241\_1 deposited under accession number ATCC 98196; the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10.

5 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- 10 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 194 to nucleotide 328;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BL187\_4 deposited under accession number ATCC 98196;
- 15 (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BL187\_4 deposited under accession number ATCC 98196;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BL187\_4 deposited under accession number ATCC 98196;
- 20 (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BL187\_4 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;
- 25 (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above; and
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID  
30 NO:13 from nucleotide 194 to nucleotide 328; the nucleotide sequence of the full length protein coding sequence of clone BL187\_4 deposited under accession number ATCC 98196; or the nucleotide sequence of the mature protein coding sequence of clone BL187\_4 deposited under accession number ATCC 98196. In other preferred embodiments, the

polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BL187\_4 deposited under accession number ATCC 98196.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13, SEQ ID NO:12 or SEQ ID NO:15.

5 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:14;
- (b) fragments of the amino acid sequence of SEQ ID NO:14; and
- 10 (c) the amino acid sequence encoded by the cDNA insert of clone BL187\_4 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14.

In one embodiment, the present invention provides a composition comprising an  
15 isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16 from nucleotide 2 to nucleotide 309;
- 20 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16 from nucleotide 131 to nucleotide 309;
- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BL249\_18 deposited under accession number ATCC 98196;
- 25 (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BL249\_18 deposited under accession number ATCC 98196;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BL249\_18 deposited under accession number ATCC 98196;
- 30 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BL249\_18 deposited under accession number ATCC 98196;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:17;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:17 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

5 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:16 from nucleotide 2 to nucleotide 309; the nucleotide sequence of SEQ ID NO:16 from nucleotide 131 to nucleotide 309; the nucleotide sequence of the full length protein coding  
10 sequence of clone BL249\_18 deposited under accession number ATCC 98196; or the nucleotide sequence of the mature protein coding sequence of clone BL249\_18 deposited under accession number ATCC 98196. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BL249\_18 deposited under accession number ATCC 98196. In yet other preferred  
15 embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:17 from amino acid 2 to amino acid 101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:16 or SEQ ID NO:18.

20 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:17;

(b) the amino acid sequence of SEQ ID NO:17 from amino acid 2 to  
25 amino acid 101;

(c) fragments of the amino acid sequence of SEQ ID NO:17; and

(d) the amino acid sequence encoded by the cDNA insert of clone  
BL249\_18 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such  
30 protein comprises the amino acid sequence of SEQ ID NO:17 or the amino acid sequence of SEQ ID NO:17 from amino acid 2 to amino acid 101.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20 from nucleotide 459 to nucleotide 539;
- 5 (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BO71\_1 deposited under accession number ATCC 98196;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BO71\_1 deposited under accession number ATCC 98196;
- 10 (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BO71\_1 deposited under accession number ATCC 98196;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BO71\_1 deposited under accession number ATCC 98196;
- 15 (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:21;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:21 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;
- 20 (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).
- 25 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:20 from nucleotide 459 to nucleotide 539; the nucleotide sequence of the full length protein coding sequence of clone BO71\_1 deposited under accession number ATCC 98196; or the nucleotide sequence of the mature protein coding sequence of clone BO71\_1 deposited under accession number ATCC 98196. In other preferred embodiments, the
- 30 polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BO71\_1 deposited under accession number ATCC 98196.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:20, SEQ ID NO:19 or SEQ ID NO:22.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:21;
- 5 (b) fragments of the amino acid sequence of SEQ ID NO:21; and
- (c) the amino acid sequence encoded by the cDNA insert of clone BO71\_1 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:21.

10 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID  
15 NO:24 from nucleotide 300 to nucleotide 512;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24 from nucleotide 372 to nucleotide 512;
- (d) a polynucleotide comprising the nucleotide sequence of the full  
length protein coding sequence of clone BO365\_2 deposited under accession  
20 number ATCC 98196;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BO365\_2 deposited under accession number ATCC 98196;
- (f) a polynucleotide comprising the nucleotide sequence of the mature  
protein coding sequence of clone BO365\_2 deposited under accession number  
25 ATCC 98196;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BO365\_2 deposited under accession number ATCC 98196;
- (h) a polynucleotide encoding a protein comprising the amino acid  
sequence of SEQ ID NO:25;
- 30 (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:25 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;



(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

5 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:24 from nucleotide 300 to nucleotide 512; the nucleotide sequence of SEQ ID NO:24 from nucleotide 372 to nucleotide 512; the nucleotide sequence of the full length protein coding sequence of clone BO365\_2 deposited under accession number ATCC 98196; or the nucleotide sequence of the mature protein coding sequence of clone BO365\_2 deposited  
10 under accession number ATCC 98196. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BO365\_2 deposited under accession number ATCC 98196.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:24, SEQ ID NO:23 or SEQ ID NO:26.

15 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:25;

(b) fragments of the amino acid sequence of SEQ ID NO:25; and

20 (c) the amino acid sequence encoded by the cDNA insert of clone BO365\_2 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:25.

In one embodiment, the present invention provides a composition comprising an  
25 isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 68 to nucleotide 328;

30 (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BV51\_1 deposited under accession number ATCC 98196;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BV51\_1 deposited under accession number ATCC 98196;

- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV51\_1 deposited under accession number ATCC 98196;
- 5 (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV51\_1 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 having biological activity;
- 10 (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above; and
- (k) a polynucleotide capable of hybridizing under stringent conditions
- 15 to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:27 from nucleotide 68 to nucleotide 328; the nucleotide sequence of the full length protein coding sequence of clone BV51\_1 deposited under accession number ATCC 98196; or the nucleotide sequence of the mature protein coding sequence of clone BV51\_1

20 deposited under accession number ATCC 98196. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BV51\_1 deposited under accession number ATCC 98196.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:27 or SEQ ID NO:29.

25 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:28;
- (b) fragments of the amino acid sequence of SEQ ID NO:28; and
- 30 (c) the amino acid sequence encoded by the cDNA insert of clone BV51\_1 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:28.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:31;
- 5 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:31 from nucleotide 57 to nucleotide 396;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BV140\_3 deposited under accession number ATCC 98196;
- 10 (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BV140\_3 deposited under accession number ATCC 98196;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV140\_3 deposited under accession number ATCC 98196;
- 15 (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV140\_3 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:32;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:32 having biological activity;
- 20 (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above; and
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

25 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:31 from nucleotide 57 to nucleotide 396; the nucleotide sequence of the full length protein coding sequence of clone BV140\_3 deposited under accession number ATCC 98196; or the nucleotide sequence of the mature protein coding sequence of clone BV140\_3 deposited under accession number ATCC 98196. In other preferred embodiments, the  
30 polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BV140\_3 deposited under accession number ATCC 98196. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:32 from amino acid 29 to amino acid 57.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:31, SEQ ID NO:30 or SEQ ID NO:33.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group  
5 consisting of:

- (a) the amino acid sequence of SEQ ID NO:32;
- (b) the amino acid sequence of SEQ ID NO:32 from amino acid 29 to amino acid 57;
- (c) fragments of the amino acid sequence of SEQ ID NO:32; and
- 10 (d) the amino acid sequence encoded by the cDNA insert of clone BV140\_3 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:32 or the amino acid sequence of SEQ ID NO:32 from amino acid 29 to amino acid 57.

15 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID  
20 NO:34 from nucleotide 132 to nucleotide 242;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BV141\_2 deposited under accession number ATCC 98196;
- (d) a polynucleotide encoding the full length protein encoded by the  
25 cDNA insert of clone BV141\_2 deposited under accession number ATCC 98196;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV141\_2 deposited under accession number ATCC 98196;
- (f) a polynucleotide encoding the mature protein encoded by the  
30 cDNA insert of clone BV141\_2 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:35;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:35 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above; and

5 (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:34 from nucleotide 132 to nucleotide 242; the nucleotide sequence of the full length protein coding sequence of clone BV141\_2 deposited under accession number ATCC 10 98196; or the nucleotide sequence of the mature protein coding sequence of clone BV141\_2 deposited under accession number ATCC 98196. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BV141\_2 deposited under accession number ATCC 98196.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ 15 ID NO:34 or SEQ ID NO:36.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- 20 (a) the amino acid sequence of SEQ ID NO:35;  
(b) fragments of the amino acid sequence of SEQ ID NO:35; and  
(c) the amino acid sequence encoded by the cDNA insert of clone BV141\_2 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:35.

25 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:37;  
(b) a polynucleotide comprising the nucleotide sequence of SEQ ID 30 NO:37 from nucleotide 28 to nucleotide 351;  
(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:37 from nucleotide 328 to nucleotide 351;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone CC194\_4 deposited under accession number ATCC 98196;

5 (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone CC194\_4 deposited under accession number ATCC 98196;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CC194\_4 deposited under accession number ATCC 98196;

10 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CC194\_4 deposited under accession number ATCC 98196;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:38;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:38 having biological activity;

15 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:37 from nucleotide 28 to nucleotide 351; the nucleotide sequence of SEQ ID NO:37 from nucleotide 328 to nucleotide 351; the nucleotide sequence of the full length protein coding sequence of clone CC194\_4 deposited under accession number ATCC 98196; or the nucleotide sequence of the mature protein coding sequence of clone CC194\_4 deposited under accession number ATCC 98196. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone CC194\_4 deposited under accession number ATCC 98196. In yet other preferred  
25 embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:38 from amino acid 56 to amino acid 108.

30 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:37 or SEQ ID NO:39.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:38;
- (b) the amino acid sequence of SEQ ID NO:38 from amino acid 56 to amino acid 108;
- (c) fragments of the amino acid sequence of SEQ ID NO:38; and
- 5 (d) the amino acid sequence encoded by the cDNA insert of clone CC194\_4 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:38 or the amino acid sequence of SEQ ID NO:38 from amino acid 56 to amino acid 108.

- 10 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:41;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID  
15 NO:41 from nucleotide 62 to nucleotide 592;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone DA136\_11 deposited under accession number ATCC 98196;
- (d) a polynucleotide encoding the full length protein encoded by the  
20 cDNA insert of clone DA136\_11 deposited under accession number ATCC 98196;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DA136\_11 deposited under accession number ATCC 98196;
- (f) a polynucleotide encoding the mature protein encoded by the  
25 cDNA insert of clone DA136\_11 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:42;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:42 having biological activity;
- 30 (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above; and
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:41 from nucleotide 62 to nucleotide 592; the nucleotide sequence of the full length protein coding sequence of clone DA136\_11 deposited under accession number ATCC 98196; or the nucleotide sequence of the mature protein coding sequence of clone DA136\_11 deposited under accession number ATCC 98196. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone DA136\_11 deposited under accession number ATCC 98196. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:42 from amino acid 61 to amino acid 119.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:41, SEQ ID NO:40 or SEQ ID NO:43.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:42;
- (b) the amino acid sequence of SEQ ID NO:42 from amino acid 61 to amino acid 119;
- (c) fragments of the amino acid sequence of SEQ ID NO:42; and
- (d) the amino acid sequence encoded by the cDNA insert of clone DA136\_11 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:42 or the amino acid sequence of SEQ ID NO:42 from amino acid 61 to amino acid 119.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

Processes are also provided for producing a protein, which comprise:

- (a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and
- (b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.



Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

#### BRIEF DESCRIPTION OF FIGURES

Fig. 1 depicts the pED6 and pNotS vectors used to deposit clones of the present invention.

#### DETAILED DESCRIPTION

##### ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Clone "AX65\_22"

A polynucleotide of the present invention has been identified as clone "AX65\_22". AX65\_22 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. AX65\_22 is a full-length clone, including  
5 the entire coding sequence of a secreted protein (also referred to herein as "AX65\_22 protein").

The nucleotide sequence of the 5' portion of AX65\_22 as presently determined is reported in SEQ ID NO:1. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:2. The predicted acid sequence of the  
10 AX65\_22 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Amino acids 1 to 20 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 21. Additional nucleotide sequence from the 3' portion of AX65\_22, including the polyA tail, is reported in SEQ ID NO:3.

15 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX65\_22 should be approximately 3500 bp.

The nucleotide sequence disclosed herein for AX65\_22 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

20

Clone "BD335\_14"

A polynucleotide of the present invention has been identified as clone "BD335\_14". BD335\_14 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was  
25 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BD335\_14 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BD335\_14 protein").

The nucleotide sequence of BD335\_14 as presently determined is reported in SEQ  
30 ID NO:56. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BD335\_14 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:57.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BD335\_14 should be approximately 3000 bp.

The predicted amino acid sequence disclosed herein for BD335\_14 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTP search protocol. The predicted BD335\_14 protein demonstrated at least some homology with sequences identified as U83511 (APXL [Homo sapiens]). Based upon homology, BD335\_14 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts three potential transmembrane domains within the BD335\_14 protein sequence, one centered around amino acid 80, another around amino acid 320, and a third around amino acid 700 of SEQ ID NO:57.

10        Clone "BG241\_1"

A polynucleotide of the present invention has been identified as clone "BG241\_1". BG241\_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. BG241\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BG241\_1 protein").

The nucleotide sequence of the 5' portion of BG241\_1 as presently determined is reported in SEQ ID NO:8. An additional internal nucleotide sequence from BG241\_1 as presently determined is reported in SEQ ID NO:9. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:10. Additional nucleotide sequence from the 3' portion of BG241\_1, including the polyA tail, is reported in SEQ ID NO:11.

The nucleotide sequence disclosed herein for BG241\_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. BG241\_1 demonstrated at least some identity with an EST identified as "zb27g08.r1 Soares parathyroid tumor NbHPA Homo sapiens" (W38781, BlastN). Based upon identity, BG241\_1 proteins and each identical protein or peptide may share at least some activity. The amino acid sequence of BG241\_1 indicates that it may be homologous to some degree with beta-transducin-like protein (L28125, BlastX; T86738, BlastN).

30        Clone "BL187\_4"

A polynucleotide of the present invention has been identified as clone "BL187\_4". BL187\_4 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. BL187\_4 is a full-length clone, including

the entire coding sequence of a secreted protein (also referred to herein as "BL187\_4 protein").

The nucleotide sequence of the 5' portion of BL187\_4 as presently determined is reported in SEQ ID NO:12. An additional internal nucleotide sequence from BL187\_4 as  
5 presently determined is reported in SEQ ID NO:13. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:14. Additional nucleotide sequence from the 3' portion of BL187\_4, including the polyA tail, is reported in SEQ ID NO:15.

The nucleotide sequence disclosed herein for BL187\_4 was searched against the  
10 GenBank database using BLASTA/BLASTX and FASTA search protocols. BL187\_4 demonstrated at least some identity with an EST identified as "EST0010 Homo sapiens cDNA clone HTN-6-15" (H48938, Fasta). Based upon identity, BL187\_4 proteins and each identical protein or peptide may share at least some activity.

15     Clone "BL249\_18"

A polynucleotide of the present invention has been identified as clone "BL249\_18". BL249\_18 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. BL249\_18 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BL249\_18  
20 protein").

The nucleotide sequence of the 5' portion of BL249\_18 as presently determined is reported in SEQ ID NO:16. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:17. The predicted acid sequence of the BL249\_18 protein corresponding to the foregoing nucleotide sequence is reported in SEQ  
25 ID NO:17. Amino acids 1 to 43 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 44. Additional nucleotide sequence from the 3' portion of BL249\_18, including the polyA tail, is reported in SEQ ID NO:18.

The nucleotide sequence disclosed herein for BL249\_18 was searched against the  
30 GenBank database using BLASTA/BLASTX and FASTA search protocols. BL249\_18 demonstrated at least some identity with an EST identified as "yj20a05.s1 Homo sapiens cDNA clone 149264 3'" (R82633, BlastN). Based upon identity, BL249\_18 proteins and each identical protein or peptide may share at least some activity.

Clone "BO71\_1"

A polynucleotide of the present invention has been identified as clone "BO71\_1". BO71\_1 was isolated from a human adult retina cDNA library using methods which are selective for cDNAs encoding secreted proteins. BO71\_1 is a full-length clone, including  
5 the entire coding sequence of a secreted protein (also referred to herein as "BO71\_1 protein").

The nucleotide sequence of the 5' portion of BO71\_1 as presently determined is reported in SEQ ID NO:19. An additional internal nucleotide sequence from BO71\_1 as presently determined is reported in SEQ ID NO:20. What applicants believe is the proper  
10 reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:21. Additional nucleotide sequence from the 3' portion of BO71\_1, including the polyA tail, is reported in SEQ ID NO:22.

The nucleotide sequence disclosed herein for BO71\_1 was searched against the  
15 GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database. The nucleotide sequence shows some weak homology with the sequence for major astrocytic phosphoprotein PEA-15 (X86809, Fasta).

Clone "BO365\_2"

20 A polynucleotide of the present invention has been identified as clone "BO365\_2". BO365\_2 was isolated from a human adult retina cDNA library using methods which are selective for cDNAs encoding secreted proteins. BO365\_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BO365\_2 protein").

25 The nucleotide sequence of the 5' portion of BO365\_2 as presently determined is reported in SEQ ID NO:23. An additional internal nucleotide sequence from BO365\_2 as presently determined is reported in SEQ ID NO:24. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:25. Amino acids 1 to 24 of SEQ ID NO:25 are a predicted  
30 leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 25. Additional nucleotide sequence from the 3' portion of BO365\_2, including the polyA tail, is reported in SEQ ID NO:26.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BO365\_2 should be approximately 2800 bp.

The nucleotide sequence disclosed herein for BO365\_2 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

5        Clone "BV51\_1"

A polynucleotide of the present invention has been identified as clone "BV51\_1". BV51\_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. BV51\_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BV51\_1  
10 protein").

The nucleotide sequence of the 5' portion of BV51\_1 as presently determined is reported in SEQ ID NO:27. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:28. The predicted acid sequence of the BV51\_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ  
15 ID NO:28. Additional nucleotide sequence from the 3' portion of BV51\_1, including the polyA tail, is reported in SEQ ID NO:29.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BV51\_1 should be approximately 970 bp.

The nucleotide sequence disclosed herein for BV51\_1 was searched against the  
20 GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "BV140\_3"

A polynucleotide of the present invention has been identified as clone "BV140\_3".  
25 BV140\_3 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. BV140\_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BV140\_3 protein").

The nucleotide sequence of the 5' portion of BV140\_3 as presently determined is  
30 reported in SEQ ID NO:30. An additional internal nucleotide sequence from BV140\_3 as presently determined is reported in SEQ ID NO:31. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:32. Additional nucleotide sequence from the 3' portion of BV140\_3, including the polyA tail, is reported in SEQ ID NO:33.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BV140\_3 should be approximately 3500 bp.

The nucleotide sequence disclosed herein for BV140\_3 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. BV140\_3  
5 demonstrated at least some identity with an EST identified as "ye33g08.r1 Homo sapiens cDNA clone 119582 5'" (T94057, BlastN). Based upon identity, BV140\_3 proteins and each identical protein or peptide may share at least some activity.

Clone "BV141\_2"

10 A polynucleotide of the present invention has been identified as clone "BV141\_2". BV141\_2 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. BV141\_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BV141\_2 protein").

15 The nucleotide sequence of the 5' portion of BV141\_2 as presently determined is reported in SEQ ID NO:34. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:35. The predicted acid sequence of the BV141\_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:35. Additional nucleotide sequence from the 3' portion of BV141\_2, including the  
20 polyA tail, is reported in SEQ ID NO:36.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BV141\_2 should be approximately 1100 bp.

The nucleotide sequence disclosed herein for BV141\_2 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were  
25 found in the database.

Clone "CC194\_4"

A polynucleotide of the present invention has been identified as clone "CC194\_4". CC194\_4 was isolated from a human adult brain cDNA library using methods which are  
30 selective for cDNAs encoding secreted proteins. CC194\_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CC194\_4 protein").

The nucleotide sequence of the 5' portion of CC194\_4 as presently determined is reported in SEQ ID NO:37. What applicants presently believe is the proper reading frame

for the coding region is indicated in SEQ ID NO:38. The predicted acid sequence of the CC194\_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:38. Amino acids 1 to 100 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 101. Additional  
5 nucleotide sequence from the 3' portion of CC194\_4, including the polyA tail, is reported in SEQ ID NO:39.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CC194\_4 should be approximately 3300 bp.

The nucleotide sequence disclosed herein for CC194\_4 was searched against the  
10 GenBank database using BLASTA/BLASTX and FASTA search protocols. CC194\_4 demonstrated at least some identity with ESTs identified as "ym10h08.s1 Homo sapiens cDNA clone 47781 3'" (H11476, BlastN) and "mc99a01.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus" (W54544, BlastN). Based upon identity, CC194\_4 proteins and each identical protein or peptide may share at least some activity.

15

#### Clone "DA136\_11"

A polynucleotide of the present invention has been identified as clone "DA136\_11". DA136\_11 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins. DA136\_11 is a full-length clone,  
20 including the entire coding sequence of a secreted protein (also referred to herein as "DA136\_11 protein").

The nucleotide sequence of the 5' portion of DA136\_11 as presently determined is reported in SEQ ID NO:40. An additional internal nucleotide sequence from DA136\_11 as presently determined is reported in SEQ ID NO:41. What applicants believe is the  
25 proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:42. Additional nucleotide sequence from the 3' portion of DA136\_11, including the polyA tail, is reported in SEQ ID NO:43.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DA136\_11 should be approximately 3800 bp.

30 The nucleotide sequence disclosed herein for DA136\_11 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. DA136\_11 demonstrated at least some identity with an EST identified as "yh11b12.s1 Homo sapiens cDNA clone 42891 3'" (R59925, BlastN). Based upon identity, DA136\_11 proteins and each identical protein or peptide may share at least some activity.



Deposit of Clones

Clones AX65\_22, BD335\_14, BG241\_1, BL187\_4, BL249\_18, BO71\_1, BO365\_2, BV51\_1, BV140\_3, BV141\_2, CC194\_4, and DA136\_11 were deposited on October 3, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98196, from which each clone comprising a particular polynucleotide is obtainable. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b). Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit.

Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNotS vector depicted in Fig. 1. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

<u>Clone</u>	<u>Probe Sequence</u>
AX65_22	SEQ ID NO:44
BD335_14	SEQ ID NO:45
30 BG241_1	SEQ ID NO:46
BL187_4	SEQ ID NO:47
BL249_18	SEQ ID NO:48
BO71_1	SEQ ID NO:49
BO365_2	SEQ ID NO:50

BV51_1	SEQ ID NO:51
BV140_3	SEQ ID NO:52
BV141_2	SEQ ID NO:53
CC194_4	SEQ ID NO:54
5 DA136_11	SEQ ID NO:55

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-  
10 dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest  
15 ambiguous bases ("N's"), if any;
- (b) It should be designed to have a  $T_m$  of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with  $g\text{-}^{32}\text{P}$  ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for  
20 labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately  $4\text{e}+6$  dpm/pmole.

25 The bacterial culture containing the pool of full-length clones should preferably be thawed and 100  $\mu\text{l}$  of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100  $\mu\text{g}/\text{ml}$ . The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the  
30 dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100  $\mu\text{g}/\text{ml}$  and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, *Bio/Technology* 10, 773-778 (1992) and in R.S. McDowell, *et al.*, *J. Amer. Chem. Soc.* 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell.

The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. "Corresponding genes" are the regions of the genome that are  
5 transcribed to produce the mRNAs from which the cDNA sequences are derived and any contiguous regions of the genome necessary for the regulated expression of such genes, including but not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the  
10 sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials.

Where the protein of the present invention is membrane-bound (e.g., is a receptor),  
15 the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

20 Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing  
25 the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most  
30 preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides.

- 5       The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

          The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of  
10 stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

	Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) <sup>‡</sup>	Hybridization Temperature and Buffer <sup>†</sup>	Wash Temperature and Buffer <sup>†</sup>
5	A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
	B	DNA:DNA	<50	T <sub>B</sub> <sup>*</sup> ; 1xSSC	T <sub>B</sub> <sup>*</sup> ; 1xSSC
	C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
	D	DNA:RNA	<50	T <sub>D</sub> <sup>*</sup> ; 1xSSC	T <sub>D</sub> <sup>*</sup> ; 1xSSC
	E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
	F	RNA:RNA	<50	T <sub>F</sub> <sup>*</sup> ; 1xSSC	T <sub>F</sub> <sup>*</sup> ; 1xSSC
10	G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
	H	DNA:DNA	<50	T <sub>H</sub> <sup>*</sup> ; 4xSSC	T <sub>H</sub> <sup>*</sup> ; 4xSSC
	I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
	J	DNA:RNA	<50	T <sub>J</sub> <sup>*</sup> ; 4xSSC	T <sub>J</sub> <sup>*</sup> ; 4xSSC
	K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
	L	RNA:RNA	<50	T <sub>L</sub> <sup>*</sup> ; 2xSSC	T <sub>L</sub> <sup>*</sup> ; 2xSSC
15	M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
	N	DNA:DNA	<50	T <sub>N</sub> <sup>*</sup> ; 6xSSC	T <sub>N</sub> <sup>*</sup> ; 6xSSC
	O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
	P	DNA:RNA	<50	T <sub>P</sub> <sup>*</sup> ; 6xSSC	T <sub>P</sub> <sup>*</sup> ; 6xSSC
	Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
20	R	RNA:RNA	<50	T <sub>R</sub> <sup>*</sup> ; 4xSSC	T <sub>R</sub> <sup>*</sup> ; 4xSSC

<sup>‡</sup> The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

<sup>†</sup> SSPE (1xSSPE is 0.15M NaCl, 10mM NaH<sub>2</sub>PO<sub>4</sub>, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

- 30 <sup>\*</sup>T<sub>B</sub> - T<sub>R</sub>: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T<sub>m</sub>) of the hybrid, where T<sub>m</sub> is determined according to the following equations. For hybrids less than 18 base pairs in length, T<sub>m</sub>(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T<sub>m</sub>(°C) = 81.5 + 16.6(log<sub>10</sub>[Na<sup>+</sup>]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na<sup>+</sup>] is the concentration of sodium ions in the hybridization buffer ([Na<sup>+</sup>] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., 5 John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 10 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an 15 expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably 20 linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the 25 protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

30 Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial

strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or  
5 enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from,  
10 e.g., Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

15 The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column  
20 containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

25 Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and  
30 InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant



methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance  
5 with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

10 The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith,  
15 including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally  
20 provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another  
25 amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be  
30 expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

## USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

### Research Uses and Utilities

10 The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease  
15 states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out"  
20 known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially  
25 binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

30 The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which

the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the  
5 protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent  
10 grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to  
15 Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

#### Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein  
20 or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention  
25 can be added to the medium in or on which the microorganism is cultured.

#### Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may  
30 induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays

for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured  
5 by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter  
10 7, Immunologic studies in Humans); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Bertagnolli, et al., *J. Immunol.* 149:3778-3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node  
15 cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon  $\gamma$ , Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

20 Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., *J. Exp. Med.* 173:1205-1211, 1991; Moreau et al., *Nature*  
25 336:690-692, 1988; Greenberger et al., *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols*  
30 *in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

#### Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for

example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or

tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of

viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient  
5 by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic  
10 acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function  
15 (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides.  
20 For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used  
25 to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II  
30 molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I  $\alpha$  chain protein and  $\beta_2$  microglobulin protein or an MHC class II  $\alpha$  chain protein and an MHC class II  $\beta$  chain protein to thereby express MHC class I or MHC class II proteins on the cell surface.



Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

10       The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, *Immunologic studies in Humans*); Herrmann et al., *Proc. Natl. Acad. Sci. USA* 78:2488-2492, 1981; Herrmann et al., *J. Immunol.* 128:1968-1974, 1982; Handa et al., *J. Immunol.* 135:1564-1572, 1985; Takai et al., *J. Immunol.* 137:3494-3500, 1986; Takai et al., *J. Immunol.* 140:508-512, 1988; Herrmann et al., *Proc. Natl. Acad. Sci. USA* 78:2488-2492, 1981; Herrmann et al., *J. Immunol.* 128:1968-1974, 1982; Handa et al., *J. Immunol.* 135:1564-1572, 1985; Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bowman et al., *J. Virology* 61:1992-1998; Takai et al., *J. Immunol.* 140:508-512, 1988; Bertagnoli et al., *Cellular Immunology* 133:327-341, 1991; Brown et al., *J. Immunol.* 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, *J. Immunol.* 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

30       Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter

7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad. Sci. USA 88:7548-7551, 1991.

#### Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent

myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of  
5 hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or  
10 *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

15 Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et  
20 al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of*  
25 *Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359,  
30 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland,

H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

#### Tissue Growth Activity

5 A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth  
10 in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of  
15 congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce  
20 differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

25 Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and  
30 other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of

congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce  
5 differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in  
10 the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve  
15 tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present  
20 invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of  
25 non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac)  
30 and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting  
5 differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described  
10 in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium ).

Assays for wound healing activity include, without limitation, those described in:  
Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year  
15 Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

#### Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related  
20 activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin  $\alpha$  family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals  
25 and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- $\beta$  group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example,  
30 United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., *Endocrinology* 91:562-572, 1972; Ling et al., *Nature* 321:779-782, 1986; Vale et al., *Nature* 321:776-779, 1986; Mason et al., *Nature* 318:659-663, 1985; Forage et al., *Proc. Natl. Acad. Sci. USA* 83:3091-3095, 1986.

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#### Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells.

- 10 Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses
- 15 against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population

20 of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

- Assays for chemotactic activity (which will identify proteins that induce or prevent
- 25 chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene
- 30 Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. *J. Clin. Invest.* 95:1370-1376, 1995; Lind et al. *APMIS* 103:140-146, 1995; Muller et al. *Eur. J. Immunol.* 25: 1744-1748; Gruber et al. *J. of Immunol.* 152:5860-5867, 1994; Johnston et al. *J. of Immunol.* 153: 1762-1768, 1994.

### Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation  
5 and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

10 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins  
15 35:467-474, 1988.

### Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of  
20 such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and  
25 development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

30 The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and



Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 5 1995.

#### Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in 10 the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat 15 inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting 20 from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

#### Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major 25 roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

30 The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the

first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

5 E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to  
10 their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention  
15 encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue  
20 in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and  
25 polynucleotides of the present invention encoding such proteins, can be used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the  
30 cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used

to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides  
5 encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

10      Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or  
15 tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

20      Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height,  
25 weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein,  
30 carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic

lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen  
5 in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

#### ADMINISTRATION AND DOSING

- 10 A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term  
15 "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11,  
20 IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention,  
25 or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.
- 30 A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be

administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be  
5 administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic  
10 factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection.  
15 Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or  
20 an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain  
25 physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

30 When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred

pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The  
5 pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone.  
10 Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not  
15 increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01  $\mu$ g to about 100 mg (preferably about 0.1mg to about 10 mg, more preferably about 0.1  $\mu$ g to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the  
20 present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous  
25 therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the  
30 carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal

antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting  
5 and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When  
10 administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also  
15 optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the  
20 developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular  
25 application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins  
30 or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-



aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns.

5 In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, 10 ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 15 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

20 In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- $\alpha$  and TGF- $\beta$ ), and insulin-like growth factor (IGF).

25 The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering 30 various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in

the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline  
5 labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without  
10 limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

15 Patent and literature references cited herein are incorporated by reference as if fully set forth.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth  
McCoy, John  
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Merberg, David  
Treacy, Maurice  
Spaulding, Vikki  
Agostino, Michael J.

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES  
ENCODING THEM

(iii) NUMBER OF SEQUENCES: 57

## (iv) CORRESPONDENCE ADDRESS:

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## (v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

## (vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:  
(B) FILING DATE:  
(C) CLASSIFICATION:

## (viii) ATTORNEY/AGENT INFORMATION:

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(B) REGISTRATION NUMBER: 41,323

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## (2) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 565 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```

GATTGTCAGT TTCCAAAAAN GAGGAGGATT TGATATTCAC TTGGCCCGNG GTGATGCNTT      60
TGAGGGTGGC CGCGTCCATC TGGTCAGAAA AGACAATCTT TTTGTTGTCA AGCTTGAGGT      120
GTGGCAGGCT TGAGATCTGG CCANACACTT GAGTGACAAT GACATCCACT TTGCTTTNTC      180
TCCACAGGTG TCCACTCCCA GGTCCAAC TG CAGANTTNGA ATTCCGCNTT CATGGCCTNT      240
GAATAGAGAC TTCTGGACTC TATAGAACCC ACTGCCTCCT GATGAAGTCC CTACTGTTCA      300
CCCTTGCAGT TTTTATGCTC CTGGCCCAAT TGGTCTCAGG TAATTGGTAT GTGAAAAAGT      360
GTCTAAACGA CGTTGGAATT TGCAAGAAGA AGTGCAAACC TGAAGAGATG CATACAAAGA      420
CTACAAGAAT TTCAACAGTA ACAGCAACAA CAGTCAACAA CAACTTTGAT GATGACTACT      480
GCTTCGATGT CTTGATGGC TCCTACCCGT TTCTCCCACT GGTGGAACAT TCCCAGCCTC      540
NGTCTCCTGC TCTAGGATCC CCGAC                                          565

```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 94 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Met Lys Ser Leu Leu Phe Thr Leu Ala Val Phe Met Leu Leu Ala Gln
1           5           10           15
Leu Val Ser Gly Asn Trp Tyr Val Lys Lys Cys Leu Asn Asp Val Gly
20           25           30
Ile Cys Lys Lys Lys Cys Lys Pro Glu Glu Met His Thr Lys Thr Thr
35           40           45
Arg Ile Ser Thr Val Thr Ala Thr Thr Val Asn Asn Asn Phe Asp Asp
50           55           60
Asp Tyr Cys Phe Asp Val Phe Asp Gly Ser Tyr Pro Phe Leu Pro Leu

```

65	70	75	80
Val	Glu	His	Ser
Gln	Pro	Xaa	Ser
Pro	Ala	Leu	Gly
Ser	Pro		
85	90		

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 92 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

AAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 60

AAAAAAAAA AAAAAAAAAA AAAAAAAAAA AA 92

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 219 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ACCTGCTGGA ACGCTCGGAC GTCCTTGCGG GCCCTGTCCA TGTGAGGTCC AGGTCATCTC 60

CCGCCACCGC AGACAAGCGC CAGGATNTGC TTTTGGGGCA AGACAGTGGC TTTGGTCTTG 120

TGAANGATCC ATGTTATTTG GCTGGTCCTG GATCTAGGTC ACTCAGTTGT TCAGAAAGAG 180

GCCAAGAAGA GATGCTGCCG CTCTTCCACC ATCTCACCC 219

## (2) INFORMATION FOR SEQ ID NO:5:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 558 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```

CGCTCATGAA GGAGGGTGGT GTGGACTCAG CCTCTGAACC CTTGATAGAA GTTTGGAGTC      60
TGGAAGCCAG TGTCTGACTA CCTACCACAT GGGCTGCACC AGGCATGTGC CTTTCCCTTG      120
CAATTGTCAC TTTAGAAAGT TTGTTGAAGC TGGGGNGTGG CCCCTCGGGA TCCTCACTGT      180
CCAGCTGCGC CTCACATACA GTGTGGGGAG GAGGTGGAGG GAAGTCATCC ATGATATACA      240
CCGGGGTTTC CTGANTCGGT GGAGGAGGTG GGGGTGGGGG AAGAGGTTC AATGTGGGGC      300
TGGACGTGGC CTTGGGGTGC GGATCCCTCA CAAACANTTC GTCTTCATAA TCCTNATGAG      360
GTNGCGGGGA GTCCCGCAGG ACAGACTCAG ATATTCGGAG GGAGATCCTC CCTGGAGTGC      420
TCGGGGCCCC AAGAGGTGTG TCTGGGTCAG AAGTGCTGCA TAAACTTGGA AGACTCTGCT      480
GTTTTTGATA GTGCTTCAGG TTTGCAAAAT CAGGGGCTGA GGATTCCTCA GGAAGGNTGT      540
CCTCTCTGGC TCGGTGGG                                     558

```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 89 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```

Met Trp Gly Trp Thr Trp Pro Trp Gly Ala Asp Pro Ser Gln Thr Xaa
1           5           10           15

Arg Leu His Asn Pro Xaa Glu Val Ala Gly Ser Pro Ala Gly Gln Thr
          20           25           30

Gln Ile Phe Gly Gly Arg Ser Ser Leu Glu Cys Ser Gly Pro Gln Glu
          35           40           45

Val Cys Leu Gly Gln Lys Cys Cys Ile Asn Leu Glu Asp Ser Ala Val
          50           55           60

Phe Asp Ser Ala Ser Gly Leu Gln Asn Gln Gly Leu Arg Ile Pro Gln

```

65	70	75	80
Glu Gly Cys Pro Leu Trp Leu Arg Gly			
85			

## (2) INFORMATION FOR SEQ ID NO:7:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 291 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GTATCCACAG TGGCCTTCCT TGNTGGTGGG CAGTGTATCC TGATGGCAGG GTACAAGTAC	60
CATTAATGAA GGGTNTGCAA CATAAAGCCT TAAAAAGACA CACACTAAGA AAAGTGTAAA	120
ACCTTGAACA TTGTTATTTA TATTTTTTAA AATGGAAAAG ATCACTATGT TTGTTGTGCT	180
AACCACTTAT TTGATTCTGT TTTGTGGTGG ACATAGATGA TTACGTTTGA GCTTTGTATT	240
TTGTGAAAAC CTTAATGAAA TGAATTCCAA AGATAAAAAA AAAAAAAAAA A	291

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 190 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

CGANGCGTCT GCACCCACAC GCTCACGAAN CATCAGGAGC CTGTCTATAG CGTATCTTTC	60
AGCCCTGATG GGAAGTACTT GGCCAGTGA TCCTTCNACA AGTGCGTCCA TATCTGGAAT	120
ACTCAGAGTG GAAATCTTGT CCACAGCTAC CGANGCACTG GCGGCATCTT CCANGTGTGC	180
TGGAACGCCC	190

## (2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 391 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```

GAGTGGAAAG GCAGGGGGAG GGGCAGGGAG CAACAGAAGG AAGAGACAAC AAGCCCAAGA      60
CAGCTTCCAT TTCAGACGGA AGGCCCCAG AAGATAGAAT TCCAGCCGAC TGAAAAACCA      120
CCCAATGAAC AAAGAAGATT TTAGAAAATA GAAAGCTGTT GGGATTACAA AGTTGCGCGT      180
TTCATCGGTA CAAACTGGTC TTTGAACCTC CTTTGTGAGA GCAATTGTAG TGTCCAAATT      240
GTTAGGGAAA ACAAAAAAAA AAAATCCCAA GGAGGAGGGT TTTTCCCCCT TCCCTGTTTG      300
GTTTATCACA GCATTTTGCT TTTTTTTTGG CACAGCTTTT TACGTTTCTT TCCATTGAGC      360
CATCACAGAG CCTGTTCCGG GTGGAAACCA A                                     391

```

(2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 62 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```

Thr Ser Phe Val Arg Ala Ile Val Val Ser Lys Leu Leu Gly Lys Thr
1           5           10           15

Lys Lys Lys Asn Pro Lys Glu Glu Gly Phe Ser Pro Phe Pro Val Trp
          20           25           30

Phe Ile Thr Ala Phe Cys Phe Phe Phe Gly Thr Ala Phe Tyr Val Ser
          35           40           45

Phe His Ser Ala Ile Thr Glu Pro Val Pro Gly Gly Asn Gln
          50           55           60

```

(2) INFORMATION FOR SEQ ID NO:11:



- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 267 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: double  
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
TCTCTCTCTC TCTCCCTCTG NACCTTTCTC ATAGTTGCTT CAGATCTTAG GTCTCAAGGG      60
CACTTTGGCG CGTAGTAAGT GCTTTATGTA AGAAGGCAGG GCAGGGGGGC TTTTACAGG      120
AGAAAAAAAA ATGACTTATA AGAGAAAGAG CCTGGAGTAT TTTTGAAAAA AAAAATAATA      180
TTTTTATGTT AAAACAATTT TAAATCTTA AAATGGCCAT CAGACATAGA GAGCTTTGTG      240
TGATTCATGT TTTAAAAAAA AAAAAA      267
```

(2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 219 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: double  
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
CTTTTAACGG TCACTCNGCC TTAAACCGTC CTGGGTGTNT GTGAGGCTGA AAGGGAAGGA      60
AGAACAGGGT CTGGGCCGCT GTGTGCTCTG CCGTCATCTC TAAAAACAA CCATACCACT      120
GAATGCTACT GTGTACTTAC AAACCACACT CATATTCGTC ACGTCATTTT ATCTTCACCC      180
CCACCTCCAA ATGAGGCTTG AAATGAANAT GAAGATGTT      219
```

(2) INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 328 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: double  
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```

AAGGGAGGGC AACAGGAAAC TCTTTATTAT GGTGATGAGA TCGACAATCT CCCCTACTGT      60
TAACCTTCGC TCCTGCACAC TTCAGTGTCC TCACTCTGTA GGGCTCGCTG GCCTGGGCTT      120
CTGCGACCCG CGATCGTCCA GGAGAGGGCA CTCGGCGCCC TTCTGGGGC GCTTCTGGGG      180
CGGAATTTGC TAGGCCGCCG TAGCAGCGGT GCCAGGTCAG AAGCCGAGCC GGCCCGCTTT      240
TCGTTCTTTA ATTGGACTCT TGGCTAAGAC GCTACCGACA CCCCGTCAGG TGGTGGAGGA      300
AGAAGGACAA CAGGGAGAGG TCGAGGGC                                     328

```

## (2) INFORMATION FOR SEQ ID NO:14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```

Ala Ala Val Ala Ala Val Pro Gly Gln Lys Pro Ser Arg Pro Ala Phe
1           5           10           15

Arg Ser Leu Ile Gly Leu Leu Ala Lys Thr Leu Pro Thr Pro Arg Gln
20          25          30

Val Val Glu Glu Glu Gly Gln Gln Gly Glu Val Glu Gly
35          40          45

```

## (2) INFORMATION FOR SEQ ID NO:15:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 127 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

AAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 60  
 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 120  
 AAAAAAA 127

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 309 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CAACAACCAT CTACAGCTGT ATTCTTGTTT CCTTGATGGC ACAATTAAAC TGTGGGACTA 60  
 TATAGATGGC ATCTTAATAA AGACTTTCAT AGTTGGATGT AAAC TTCATG CCCTCTTTAC 120  
 TCTTGCCCAA GCTGAGGATT CTGTCTTTGT TATAGTGAAT AAAGAAAAC CAGATATATT 180  
 TCAGCTGGTT TCAGTGAAC TGCCAAAATC CTCAAGCCAG GAAGTAGAAG CCAAGGAGCT 240  
 GTCCTTTGTT TTGGATTACA TAAACCAAGTC ACCCAAGTGC ATTGCCTTTG GAAACGAGGG 300  
 AGTATATGT 309

## (2) INFORMATION FOR SEQ ID NO:17:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 101 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Asn His Leu Gln Leu Tyr Ser Cys Ser Leu Asp Gly Thr Ile Lys Leu  
 1 5 10 15  
 Trp Asp Tyr Ile Asp Gly Ile Leu Ile Lys Thr Phe Ile Val Gly Cys  
 20 25 30  
 Lys Leu His Ala Leu Phe Thr Leu Ala Gln Ala Glu Asp Ser Val Phe

35	40	45
Val Ile Val Asn Lys Glu Lys Pro Asp Ile Phe Gln Leu Val Ser Val		
50	55	60
Lys Leu Pro Lys Ser Ser Ser Gln Glu Val Glu Ala Lys Glu Leu Ser		
65	70	75
Phe Val Leu Asp Tyr Ile Asn Gln Ser Pro Lys Cys Ile Ala Phe Gly		
85	90	95
Asn Glu Gly Val Tyr		
100		

## (2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 282 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

AAATGATTTT ACCGAAAAAG TCCAGGATAC AAGTAACACA GGTTTAGGAG AAGACATTAT	60
ACATCAGTTG TCAAAATCTG AAGAAAAAGA ACTGAGAAAA TTTAGGAAAA TAGACTACAG	120
CTGGATAGCT GCCCTTTAAG CCTTGGAGAT GGGGAGGATC CTTGGACTTT GTGTTTTTGA	180
TTGTATGTTG ATATTCTAAA AACATCTATT TTAATGTTAT TTCTGTTCTA AAAATAAGAT	240
AATAAATATT AACAACTTT AAAAAAAAAA AAAAAAAAAA AA	282

## (2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 137 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GNGGGGGAGG ATGAATANTC GGAAGCTGNN GCGGCNGCGG GGANCCAANG AAGAGGTTCC	60
---	----

GNACCCNGCT TACGAACCGN GGACTCTTGA CTNCCCACNC CCTGAACNCT CNCCTCCAAA 120

NGCGTCATGG ATGGAAT 137

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Met Asp Cys Glu Leu Lys Met Gly Gly Asp Val Arg Gln Thr Arg Thr  
1 5 10 15

Glu Asn Pro Ser Ser Ser Cys Asp Leu Ala Val  
20 25

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 99 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

AGAGAGGCAG ATCCCAATG AGGGGTCAGG ACGGGTCTTG GCTGCACATN CTGGNNTCAT 60

ANTNATCCCA TGGGGAGCAG CACNTTATGA AAAAAAAAAA 99

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 219 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

ATTANCCACT GCACCTGGCT GGTGTCTCCA TTTTACANAT NAGGCTGTCA CCCCCCAATA 60  
 TCACACAGCC AAGTGGCAGA NTGTGTTC AATGCTGGCA GTCAGGCCAT GCTCTGTCTG 120  
 AATCCAAACT CTGCCACTTT CTAAGTGTGT GTTCTCGGGC AGGTTATTTA CCAACTTTGA 180  
 AGTCCATTTT CTTATCCCTA AAAGANGGCT GANAAGCTC 219

## (2) INFORMATION FOR SEQ ID NO:24:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

TCGGCTTTCC ATRACTGGGG CCTGGGCCAG AGCAGGGGCT GGGGGGNTCA GTGGCATCCG 60  
 ACGACTGGAA GCTGTTCCAT CCGGTACCAT CCAGGCTTGG GCCTGAAGGG GGTGTGGGGT 120  
 CACTGAGGCC TGAGGGGAAA GCAGGAGAGA GGTGAAGGAG CTGGGTTGAC CTTGCAGAGG 180  
 CCAGAGAGCC GAGGGGCCAT GTGTGCTGGC ATGGGGCTCC CTGCCCCTTT CTGAGGCTCA 240  
 GCACGGAGGG GAGAAACCCA CATTTTCAGA GGAACAGC AGCAGAGCAG AACCAGTAAC 300  
 CAAGATCCCG GCAACCCCTT GTGCTGACCC CACACACGCT TCCCCCTTC CTGGCCAGGC 360  
 CACTCCAAAG CTCTGTGCAC ACAGACAATA GACATCAGGA CTTTCATCTT CACTCGTCAT 420  
 CTGGCAGCAG AGAGCCTGCA GGGCTGGGCT GCAGGGAGAA GAGTTCCTTT CCTCAGCAT 480  
 CCAGGCAAGG GGAGAGCAGC TCTGTGCCTG CC 512

## (2) INFORMATION FOR SEQ ID NO:25:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 71 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```

Pro Arg Ser Arg Gln Pro Leu Val Leu Thr Pro His Thr Leu Pro Leu
1           5           10           15

Phe Leu Ala Arg Pro Leu Gln Ser Ser Val His Thr Asp Asn Arg His
          20           25           30

Gln Asp Phe His Leu His Ser Ser Ser Gly Ser Arg Glu Pro Ala Gly
          35           40           45

Leu Gly Cys Arg Glu Lys Ser Ser Phe Pro His Ala Ser Arg Gln Gly
          50           55           60

Glu Ser Ser Ser Val Pro Ala
          65           70

```

## (2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 106 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```

AAAAACAAAA ACAAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA    60
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAA                      106

```

## (2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 328 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```

AGACTTCGAA TTCGGCCTTC ATGGCCTARA AAAACTGATT CACCTGGCAG AGACCTACCC    60
CATCCACATG CACAGCCAGC TGGACCACCT TAGCCTCTAT TACTGCAGGT GTACTCTGCC    120

```

AGAGAATCCA AACAAATCACA CCCTCCAGTA CTGGAAGGAC CACAACATCG TGACAGCAGA 180  
 AGTCCACTGG GCTAACCTGA CTGTCAGTGA ATGCCAGGAG ATGCATGGAG AGTTCATGGG 240  
 ATCTGCGTGC GGCCATCATG GACCCTACAC TCCTGATGTC CTCTTTTGGT CCTGTATTCT 300  
 CTTTTTCACC ACCTTCATCC TCTCAAGC 328

## (2) INFORMATION FOR SEQ ID NO:28:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 87 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met	His	Ser	Gln	Leu	Asp	His	Leu	Ser	Leu	Tyr	Tyr	Cys	Arg	Cys	Thr
1				5					10					15	
Leu	Pro	Glu	Asn	Pro	Asn	Asn	His	Thr	Leu	Gln	Tyr	Trp	Lys	Asp	His
			20					25					30		
Asn	Ile	Val	Thr	Ala	Glu	Val	His	Trp	Ala	Asn	Leu	Thr	Val	Ser	Glu
			35				40					45			
Cys	Gln	Glu	Met	His	Gly	Glu	Phe	Met	Gly	Ser	Ala	Cys	Gly	His	His
		50				55					60				
Gly	Pro	Tyr	Thr	Pro	Asp	Val	Leu	Phe	Trp	Ser	Cys	Ile	Leu	Phe	Phe
65					70					75				80	
Thr	Thr	Phe	Ile	Leu	Ser	Ser									
						85									

## (2) INFORMATION FOR SEQ ID NO:29:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 326 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:



NAAATGTATT TATATGTATG TCTTATTATA NACAAGGCAG ATTTCCCCTG GAATAAAAAGT 60  
 CTAGAATGTA CTGCTTAATT TNANACATGT GTGCAGGCAA TATTATCTGT GAGTGAAAAG 120  
 TGGAATAANA CGTGGATTGG GTCAACTGAT TATCAGCTTG TTAGGAGTCC TCTGTGTGAG 180  
 ACATGGTGGT ATAATTGTGA AGTTCTCACT GTATGTGGAT GTTCATGTGA AAGATAGTAC 240  
 TTTCTTCCCG TAAATATCTT TTGATTTCCA TTTGTATGGA ATCCCAATGA ATGTATCTTT 300  
 GGAAAACAAA AAAAAAAAAA AAAAAA 326

## (2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 194 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

AAGTCTCATT CTCAAGAGTG ATGCTGCAAA ACCCCTTTTG GGCCATGATG CTGTNATCCA 60  
 GGCTTTAGCA CANAAAGGTC TTTATGTCAC TGACCAGGAA AAATTGGTAA CTGAACGANA 120  
 TCTCCNCAAG AAACCCNTAC AGATGAGTGC ACATTTGGGC CATGATCGAT ACCNCATGAT 180  
 GGCTTATACT GTAT 194

## (2) INFORMATION FOR SEQ ID NO:31:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 396 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

TTCATTTTTA CTGTCCTGAT GTTGTGAGAT TAGAGGATAT TTGTTTGAAA GAACTATGT 60  
 CTTTGGCTGA TAGCCTGTAT AATCTGCAGC TGATTCAAGA ATTTTGCCAA GAATACTTGA 120  
 ACCAGTGTG CCATTCANT CTGGAAGATA TGCTCTATGC TGCTTCATCC ATAAAGAGTA 180

ATTATTTGGT GTTCATGGCG GAACTGTTCT GGTGGTTTGA AGTGGTGAAG CCGTCTTTTG 240  
 TACAGCCTCG TGTTGTTTCGT CCACAAGGAG CTGAACCTGT AAAAGATATG CCTTCAATTC 300  
 CTGTCTTGAA TGCTGCCAAA AGAAATGTCT TAGATAGTAG TTCTGACTTC CCTTCAAGTG 360  
 GGGAAGGAGC TACATTTACA CAGTCTCATC TCGAGG 396

## (2) INFORMATION FOR SEQ ID NO:32:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met	Ser	Leu	Ala	Asp	Ser	Leu	Tyr	Asn	Leu	Gln	Leu	Ile	Gln	Glu	Phe	1	5	10	15
Cys	Gln	Glu	Tyr	Leu	Asn	Gln	Cys	Cys	His	Phe	Xaa	Leu	Glu	Asp	Met	20	25	30	
Leu	Tyr	Ala	Ala	Ser	Ser	Ile	Lys	Ser	Asn	Tyr	Leu	Val	Phe	Met	Ala	35	40	45	
Glu	Leu	Phe	Trp	Trp	Phe	Glu	Val	Val	Lys	Pro	Ser	Phe	Val	Gln	Pro	50	55	60	
Arg	Val	Val	Arg	Pro	Gln	Gly	Ala	Glu	Pro	Val	Lys	Asp	Met	Pro	Ser	65	70	75	80
Ile	Pro	Val	Leu	Asn	Ala	Ala	Lys	Arg	Asn	Val	Leu	Asp	Ser	Ser	Ser	85	90	95	
Asp	Phe	Pro	Ser	Ser	Gly	Glu	Gly	Ala	Thr	Phe	Thr	Gln	Ser	His	Leu	100	105	110	
Glu																			

## (2) INFORMATION FOR SEQ ID NO:33:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 336 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

AATTTGATGA TGACCAGAAA GTATGCTGTG GTTCTTTTTT AAGGATGATC AAAAAGCAGA	60
AAATGATATG GCAATGAAAC GGGCAGNTTT GTTGGAGAAA AGATTAAGAA GGGAAAAGGA	120
AANTCAGCTC CGGAAACAAC AGTTGGAAGC AGAAATGGAG CATAAGAAGG AGGAAACAAG	180
GCGTAAAACT GAGGAAGAAC GTCAGAAGAA AGAAGATGAG AGAGCACGCA GAGAATTTAT	240
TAGGCAAGAA TATATGAGGC GGAAACAAC TAACTAATG GAAGATATGG ATACAGTAAT	300
TAAACCCCGT CCTCAAGTAG TAAAAA AAAA	336

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 228 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GCGATTGAAT TCTAGACCTG CCTCGAGCTC ACACCTGGAT TATCTCAGTA GTTTCCTAAC	60
TGGTTTCCTT GTTTCATTG TTGCCTCCTT CTGTCTACTC TCAATATAAC AGCTAGAACA	120
ATCCTTTTAC AATGGAATTC AGATCATGTT TACCCCTCTG TTCAAATTCT CCAGTGACTT	180
TCCAGTTTTT ACATGATCTG GCTCCTACTA CCTGTCTCAC TGTGTTTC	228

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Met Glu Phe Arg Ser Cys Leu Pro Leu Cys Ser Asn Ser Pro Val Thr  
 1                      5                      10                      15  
 Phe Gln Phe Leu His Asp Leu Ala Pro Thr Thr Cys Leu Thr Val Phe  
                     20                      25                      30  
 Pro Thr Thr Leu Leu  
                     35

## (2) INFORMATION FOR SEQ ID NO:36:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 185 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GGCCTNTNGG GGGGTGAGAG GCAAGGGAAG TGATAGCATT AAGAGAAATA CCTAATGTAG      60  
 ATTATGGGTT GATGGGGGCA GCAAACCACC ATGGCACATG TGTACCTATG TAACAAACCT      120  
 GCACATNTTG CACATATATC CCAGAACTTA AAGTATAATT AAAGAAAAAG AAAAAAAAAA      180  
 AAAAAA      185

## (2) INFORMATION FOR SEQ ID NO:37:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 351 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GGCTTTGACC GCTATCGCCA GGAGTGGATG GACTATGGCT GTGCACAGGA GGCAGAGGGC      60  
 AGGATGTGCG AGGACTTCCA GGATGAGGAC CACGACTCAG CCTCCCCTGA CACTTCCTTC      120  
 AGCCCCTATG ATGGAGACCT CACCAMTACC TCCTCCTCCC TCTTCATCGA CAGCCTCACC      180

ACAGAAGATG ACACCAAGTT GAATCCCTAT GCAGGAGGAG ACGGCCTTCA GAACAACCTG 240  
 TCCCCAAGA CAAAGGGCAC TCCTGTGCAC CTGGGCACCA TCGTGGGCAT CGTGCTGGCA 300  
 GTCTCTCTCG TGGCGGCCAT CATCTGGCT GGAATTTACA TCAATGGCCA C 351

## (2) INFORMATION FOR SEQ ID NO:38:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 108 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Met Asp Tyr Gly Cys Ala Gln Glu Ala Glu Gly Arg Met Cys Glu Asp  
 1 5 10 15  
 Phe Gln Asp Glu Asp His Asp Ser Ala Ser Pro Asp Thr Ser Phe Ser  
 20 25 30  
 Pro Tyr Asp Gly Asp Leu Thr Xaa Thr Ser Ser Ser Leu Phe Ile Asp  
 35 40 45  
 Ser Leu Thr Thr Glu Asp Asp Thr Lys Leu Asn Pro Tyr Ala Gly Gly  
 50 55 60  
 Asp Gly Leu Gln Asn Asn Leu Ser Pro Lys Thr Lys Gly Thr Pro Val  
 65 70 75 80  
 His Leu Gly Thr Ile Val Gly Ile Val Leu Ala Val Leu Leu Val Ala  
 85 90 95  
 Ala Ile Ile Leu Ala Gly Ile Tyr Ile Asn Gly His  
 100 105

## (2) INFORMATION FOR SEQ ID NO:39:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 179 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GTGTCAGCC CCTTCCTTTC CCCNGACCTA AANATAAAAG ACAAGGCAAA GCCCGNATAA	60
TTTTAAGACG GTTTTTTAGG ANATTAGTCC ACNATTTTNT TGGTTTGATG GTTTTCNGAA	120
ATAAAGTCCC TTTCCTNGCT CCAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA	179

## (2) INFORMATION FOR SEQ ID NO:40:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GGAAACTCAN CCACCTGTGA CAAATTTGAG TGTCTCTGTT GAAAACCTCT GCACAGTAAT	60
ATGGACATGG AATCCACCCG AGGGAGCCAG CTCAAATTGT AGTCTATGGT ATTTTAGTCA	120
TTTTGGCGAC AAACAAGATA AGAAAATAGC TCCGGAAACT CGTCGTTCAA TAGAAGTACC	180
CCTGAATGAG AGGATTTGTC TGCAAGTGGG GTCCCAAGTGT ANCACCAATG AGAGTGAGAA	240
GCCTAGCATT TTGGTTGAAA AATGCATCTC ACCCCCAGAA GGTGATCCTG AATCTGCTGT	300
GACTGAGCTT CAATGCATTT GGCACAACCT GAGCTACATG	340

## (2) INFORMATION FOR SEQ ID NO:41:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 592 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TTGTTCCCTTT GATCTGACCA AAGTGAAGGA TTCCAGTTT GAACAACACA GTGTCCAAAT	60
AATGGTCAAG GATAATGCAG GAAAAATTAA ACCATCCTTC AATATAGTGC CTTTAACTTC	120
CCGTGTGAAA CCTGATCCTC CACATATTAA AAACCTCTCC TTCCACAATG ATGACCTATA	180

TGTGCAATGG GAGAATCCAC AGAATTTTAT TAGCAGATGC CTATTTTATG AAGTAGAAGT 240  
 CAATAACAGC CAAACTGAGA CACATAATGT TTTCTACGTC CAAGAGGCTA AATGTGAGAA 300  
 TCCAGAATTT GAGAGAAATG TGGAGAATAC ATCTTGTTTC ATGGTCCCTG GTGTTCTTCC 360  
 TGATACTTTG AACACAGTCA GAATAAGAGT CAAAACAAAT AAGTTATGCT ATGAGGATGA 420  
 CAAACTCTGG AGTAATTGGA GCCAAGAAAT GAGTATAGGT AAGAAGCGCA ATTCCACACT 480  
 CTACATAACC ATGTTACTCA TTGTTCCAGT CATCGTCGCA GGTGCAATCA TAGTACTCCT 540  
 GCTTTACCTA AAAAGGCTCA AGATTATTAT ATTCCCTCCA ATTCCTGATC CT 592

## (2) INFORMATION FOR SEQ ID NO:42:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Met Val Lys Asp Asn Ala Gly Lys Ile Lys Pro Ser Phe Asn Ile Val  
 1 5 10 15  
 Pro Leu Thr Ser Arg Val Lys Pro Asp Pro Pro His Ile Lys Asn Leu  
 20 25 30  
 Ser Phe His Asn Asp Asp Leu Tyr Val Gln Trp Glu Asn Pro Gln Asn  
 35 40 45  
 Phe Ile Ser Arg Cys Leu Phe Tyr Glu Val Glu Val Asn Asn Ser Gln  
 50 55 60  
 Thr Glu Thr His Asn Val Phe Tyr Val Gln Glu Ala Lys Cys Glu Asn  
 65 70 75 80  
 Pro Glu Phe Glu Arg Asn Val Glu Asn Thr Ser Cys Phe Met Val Pro  
 85 90 95  
 Gly Val Leu Pro Asp Thr Leu Asn Thr Val Arg Ile Arg Val Lys Thr  
 100 105 110  
 Asn Lys Leu Cys Tyr Glu Asp Asp Lys Leu Trp Ser Asn Trp Ser Gln  
 115 120 125  
 Glu Met Ser Ile Gly Lys Lys Arg Asn Ser Thr Leu Tyr Ile Thr Met  
 130 135 140

Leu Leu Ile Val Pro Val Ile Val Ala Gly Ala Ile Ile Val Leu Leu  
 145 150 155 160

Leu Tyr Leu Lys Arg Leu Lys Ile Ile Ile Phe Pro Pro Ile Pro Asp  
 165 170 175

Pro

(2) INFORMATION FOR SEQ ID NO:43:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 285 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

TGTGGGAAAT TAGTAGGCTC ATTTACTGTT TTAGGTCTAG CNTATGTGGA TTTTTCCTA 60  
 ACATACTTAA GCAAACCCAG NGTCAGGATG GNAATTNTTA TTCTTTCGTT CAGTTAAGTT 120  
 TTTCCNTTCA TNNGGGCACT GAAGGGATAT GTGAAACAAT GTTAACATTT TTGGTAGTNT 180  
 TCAACCAGGG ATTGTTTCTG TTTAACTTCT TATAGGAAAG CTTGAGTAAA ATAAATATTG 240  
 TCTTTTGTGA TGTCACCCAA AAAAAAAAAA AAAAAAAAAA AAAAA 285

(2) INFORMATION FOR SEQ ID NO:44:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 28 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TAGGTTTGCA CTTCTTCTTG CAAATTCC 28

(2) INFORMATION FOR SEQ ID NO:45:

- (i) SEQUENCE CHARACTERISTICS:



- (A) LENGTH: 28 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CAATATCTGA GTCTGTCCTG CGGGACTC

28

- (2) INFORMATION FOR SEQ ID NO:46:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CGGCTCTGTG ATGGCTGAAT GGAAAGAA

28

- (2) INFORMATION FOR SEQ ID NO:47:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

AGAGTCCAAT TAAAGAACGA AAAGCGGG

28

- (2) INFORMATION FOR SEQ ID NO:48:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 base pairs

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

CTCAGCTTGG GCAAGAGTAA AGAGGGCA

28

- (2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TATTTAAGAT GCTGTGTAAG CCTCTCGC

28

- (2) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

TTCTGTGTGC ACAGAGCTTT GGAGTGGC

28

- (2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 base pairs
  - (B) TYPE: nucleic acid

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

GTTGGATTCT CTGGCAGAGT ACACCTGC

28

- (2) INFORMATION FOR SEQ ID NO:52:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GAGGCATATC TTTTACAGGT TCAGCTCC

28

- (2) INFORMATION FOR SEQ ID NO:53:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
  - (A) DESCRIPTION: /desc = "oligonucleotide"

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

CCAGTGAGAC AGGTAGTAGG AGCCAGAT

28

- (2) INFORMATION FOR SEQ ID NO:54:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

AGTAAATTCC AGCCAGGATG ATGGCCGC

28

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

TGAGTGTGGA ATTGCGCTTC TTACCTAT

28

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2949 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

ACCTGCTGGA ACGCTCGGAC GTCCTTGCGG GCCCTGTCCA TGTGAGGTCC AGGTCATCTC 60

CCGCCACCGC AGACAAGCGC CAGGATGTGC TTTTGGGGCA AGACAGTGGC TTTGGTCTTG 120

TGAAGGATCC ATGTTATTTG GCTGGTCCTG GATCTAGGTC ACTCAGTTGT TCAGAAAGAG 180

GCCAAGAAGA GATGCTGCCG CTCTTCCACC ATCTCACCCC TCGTTGGGGT GGTTCAGGCT 240

GCAAAGCCAT TGGTGATTCC TCCGTTCTTA GTGAATGTCC TGGAACCCCTG GACCATCAGA 300

GGCAAGCCAG TAGGACACCC TGCCCCAGGC CACCACTGGC AGGAACGCAA GGGCTGGTCA	360
CAGACACCAG GGCTGCACCC CTGACCCCAA TTGGCACCCC TCTGCCTTCA GCCATTCCCT	420
CTGGCTACTG CTCACAGGAC GGTACAGACAG GCGACAGCC TCTCCCGCCC TACACCCCTG	480
CCATGATGCA CAGAAGCAAT GGTCACACCC TGACCCAGCC TCCCGGTCCA AGAGGCTGTG	540
AGGCGCATGG CCCAGAGCAT GGGGTAGAAG AGGGAACGAG GAAGAGGGTC TCGCTGCCTC	600
AGTGGCCACC TCCTTCTCGA GCAAAGTGGG CCCACGCAGC CAGAGAGGAC AGCCTTCCTG	660
AGGAATCCTC AGCCCTGAT TTTGCAAACC TGAAGCACTA TCAAAAACAG CAGAGTCTTC	720
CAAGTTTATG CAGCACTTCT GACCCAGACA CACCTCTTGG GGCCCCGAGC ACTCCAGGGA	780
GGATCTCCCT CCGAATATCT GAGTCTGTCC TGCGGGACTC CCCGCCACCT CATGAGGATT	840
ATGAAGACGA AGTGTTTGTG AGGGATCCGC ACCCAAGGC CACGTCCAGC CCCACATTTG	900
AACCTCTTCC CCCACCCCCA CCTCCTCCAC CGAGTCAGGA AACCCCGGTG TATAKCATGG	960
ATGACTTCCC TCCACCTCCT CCCACACTG TATGTGAGGC GCAGCTGGAC AGTGAGGATC	1020
CCGAGGGGCC ACGCCCCAGC TTCAACAAAC TTTCTAAAGT GACAATGCA AGGGAAAGGC	1080
ACATGCCTGG TGCAGCCCAT GTGGTAGGTA GTCAGACACT GGCTTCCAGA CTCCAAACTT	1140
CTATCAAGGG TTCAGAGGCT GAGTCCACAC CACCCTCCTT CATGAGCGTT CACGCCCAAC	1200
TTGCTGGGTC TCTTGGTGGG CAGCCAGCAC CCATCCAGAC TCAAAGCCTC AGCCATGATC	1260
CAGTCAGTGG AACTCAGGGT TTAGAAAAGA AAGTCAGTCC TGATCCTCAG AAGAGTTCAG	1320
AAGACATCAG AACAGAGGCT TTGGCCAAGG AAATTGTCCA CCAAGACAAA TCTCTAGCAG	1380
ACATTTTGA TCCAGACTCC AGGCTGAAGA CAACAATGGA CCTGATGGAA GGTMTGTTC	1440
CCCAGATGT GAACTTGCTG AAGGAAAACA GTGTAAAGAG GAAGGCCATA CAGAGAACTG	1500
TCAGCTCTTC AGGATGTGAA GGCAAGAGGA ATGAAGACAA GGAAGCAGTG AGCATGTTGG	1560
TTAACTGCCC TGCCTACTAC AGTGTGTCTG CTCCAAGGC TGAGCTACTG AACAAAATCA	1620
AAGAGATGCC AGCAGAAGTG AATGAGGAAG AGGAACAGGC AGATGTCAAT GAAAAGAAGG	1680
CTGAGCTCAT TGAAGTCTC ACCCACAAGC TGGAGACCCT CCAGGAGGCG AAGGGGAGCC	1740
TGCTCACGGA CATCAAGCTC AACAAACGCC TGGGAGAAGA GGTGGAGGCT CTGATCAGCG	1800
AGCTCTGCAA GCCCAATGAG TTTGACAAGT ATAGGATGTT CATAGGGGAT TTGGACAAGG	1860
TGGTCAACCT GCTGCTCTCC CTCTCGGGGC GTCTAGCCCG TGTTGAGAAT GTCCTTAGCG	1920
GCCTTGGTGA AGATGCCAGT AATGAAGAAA GGAGCTCTCT TTACGAGAAA AGGAAGATCC	1980

TGGCTGGTCA GCATGAGGAT GCCCCGGAGC TGAAGGAGAA CCTGGATCGC AGGGAGCGAG 2040  
 TAGTGCTGGG CATCTTGGCC AATTACCTTT CAGAGGAGCA GCTCCAGGAC TACCAGCACT 2100  
 TCGTGAAAT GAAGTCCAG CTCCTCATTG AGCAACGGAA GCTGGATGAC AAGATCAAGC 2160  
 TGGGCCAGGA GCAGGTCAAG TGTCTGCTGG AGAGCCTGCC CTCAGATTTC ATTCCCAAGG 2220  
 CTGGGGCCCT GGCTCTGCCC CCAAACCTCA CGAGTGAGCC CATTCCTGCT GGGGGCTGTA 2280  
 CTTTCAGTGG TATTTTCCCA ACATTAACT CTCCACTTTA ACCTCTTCTA AAATACCCAA 2340  
 CCAAAAGATC ACTGTTTCTC TCAACACTAT TTAATCTGAA AAATGTTTCA GTACAAACCA 2400  
 CTGTTTGAAC TATCTGGGTT ATTGGTGTTC GTTCCTGATG AAAGGAAAAA AATTCTCTCC 2460  
 AGGAGGAAGC CTTTTTCCTT CTGCCCCTTC CTGATTGATC TTCTGAGAGC TCGAATGCTG 2520  
 CTGGACACGT ACCCCTTCTA TTATTACTTT GTAGTAGAAA GAAAGTTAAT GAAACTGAGA 2580  
 ACTGATTGGA GGGTGTTTGA TCATTTAGTT TTTAACAGGC TGAGGCAACA TGGATCAGTG 2640  
 TGTGTCCCCC TCAGGAATGT ATCCACAGTG GCCTTCCTTG CTGGTGGGCA GTGTATCCTG 2700  
 ATGGCAGGGT ACAAGTACCA TTAATGAAGG GTCTGCAACA TAAAGCCTTA AAAAGACACA 2760  
 CACTAAGAAA ACTGTAAAC CTTGAACATT GTTATTTATA TTTTTTAAAA TGGAAAAGAT 2820  
 CACTATGTTT GTTGTGCTAA CCACTTATTT GATTCTGTTT TGTGGTGGAC ATAGATGATT 2880  
 ACGTTTGAGC TTTGTATTTT GTGAAAACCT TAATGAAATG AATTCCAAAG ATAAAAAAA 2940  
 AAAAAAAA 2949

## (2) INFORMATION FOR SEQ ID NO:57:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 709 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Met Leu Pro Leu Phe His His Leu Thr Pro Arg Trp Gly Gly Ser Gly  
 1 5 10 15  
 Cys Lys Ala Ile Gly Asp Ser Ser Val Pro Ser Glu Cys Pro Gly Thr  
 20 25 30

Leu Asp His Gln Arg Gln Ala Ser Arg Thr Pro Cys Pro Arg Pro Pro  
 35 40 45  
 Leu Ala Gly Thr Gln Gly Leu Val Thr Asp Thr Arg Ala Ala Pro Leu  
 50 55 60  
 Thr Pro Ile Gly Thr Pro Leu Pro Ser Ala Ile Pro Ser Gly Tyr Cys  
 65 70 75 80  
 Ser Gln Asp Gly Gln Thr Gly Arg Gln Pro Leu Pro Pro Tyr Thr Pro  
 85 90 95  
 Ala Met Met His Arg Ser Asn Gly His Thr Leu Thr Gln Pro Pro Gly  
 100 105 110  
 Pro Arg Gly Cys Glu Gly Asp Gly Pro Glu His Gly Val Glu Glu Gly  
 115 120 125  
 Thr Arg Lys Arg Val Ser Leu Pro Gln Trp Pro Pro Pro Ser Arg Ala  
 130 135 140  
 Lys Trp Ala His Ala Ala Arg Glu Asp Ser Leu Pro Glu Glu Ser Ser  
 145 150 155 160  
 Ala Pro Asp Phe Ala Asn Leu Lys His Tyr Gln Lys Gln Gln Ser Leu  
 165 170 175  
 Pro Ser Leu Cys Ser Thr Ser Asp Pro Asp Thr Pro Leu Gly Ala Pro  
 180 185 190  
 Ser Thr Pro Gly Arg Ile Ser Leu Arg Ile Ser Glu Ser Val Leu Arg  
 195 200 205  
 Asp Ser Pro Pro Pro His Glu Asp Tyr Glu Asp Glu Val Phe Val Arg  
 210 215 220  
 Asp Pro His Pro Lys Ala Thr Ser Ser Pro Thr Phe Glu Pro Leu Pro  
 225 230 235 240  
 Pro Pro Pro Pro Pro Pro Pro Ser Gln Glu Thr Pro Val Tyr Xaa Met  
 245 250 255  
 Asp Asp Phe Pro Pro Pro Pro Pro His Thr Val Cys Glu Ala Gln Leu  
 260 265 270  
 Asp Ser Glu Asp Pro Glu Gly Pro Arg Pro Ser Phe Asn Lys Leu Ser  
 275 280 285  
 Lys Val Thr Ile Ala Arg Glu Arg His Met Pro Gly Ala Ala His Val  
 290 295 300  
 Val Gly Ser Gln Thr Leu Ala Ser Arg Leu Gln Thr Ser Ile Lys Gly  
 305 310 315 320  
 Ser Glu Ala Glu Ser Thr Pro Pro Ser Phe Met Ser Val His Ala Gln

	325		330		335
Leu Ala Gly Ser Leu Gly Gly Gln Pro Ala Pro Ile Gln Thr Gln Ser					
	340		345		350
Leu Ser His Asp Pro Val Ser Gly Thr Gln Gly Leu Glu Lys Lys Val					
	355		360		365
Ser Pro Asp Pro Gln Lys Ser Ser Glu Asp Ile Arg Thr Glu Ala Leu					
	370		375		380
Ala Lys Glu Ile Val His Gln Asp Lys Ser Leu Ala Asp Ile Leu Asp					
	385		390		395
Pro Asp Ser Arg Leu Lys Thr Thr Met Asp Leu Met Glu Gly Leu Phe					
	405		410		415
Pro Arg Asp Val Asn Leu Leu Lys Glu Asn Ser Val Lys Arg Lys Ala					
	420		425		430
Ile Gln Arg Thr Val Ser Ser Ser Gly Cys Glu Gly Lys Arg Asn Glu					
	435		440		445
Asp Lys Glu Ala Val Ser Met Leu Val Asn Cys Pro Ala Tyr Tyr Ser					
	450		455		460
Val Ser Ala Pro Lys Ala Glu Leu Leu Asn Lys Ile Lys Glu Met Pro					
	465		470		475
Ala Glu Val Asn Glu Glu Glu Glu Gln Ala Asp Val Asn Glu Lys Lys					
	485		490		495
Ala Glu Leu Ile Gly Ser Leu Thr His Lys Leu Glu Thr Leu Gln Glu					
	500		505		510
Ala Lys Gly Ser Leu Leu Thr Asp Ile Lys Leu Asn Asn Ala Leu Gly					
	515		520		525
Glu Glu Val Glu Ala Leu Ile Ser Glu Leu Cys Lys Pro Asn Glu Phe					
	530		535		540
Asp Lys Tyr Arg Met Phe Ile Gly Asp Leu Asp Lys Val Val Asn Leu					
	545		550		555
Leu Leu Ser Leu Ser Gly Arg Leu Ala Arg Val Glu Asn Val Leu Ser					
	565		570		575
Gly Leu Gly Glu Asp Ala Ser Asn Glu Glu Arg Ser Ser Leu Tyr Glu					
	580		585		590
Lys Arg Lys Ile Leu Ala Gly Gln His Glu Asp Ala Arg Glu Leu Lys					
	595		600		605
Glu Asn Leu Asp Arg Arg Glu Arg Val Val Leu Gly Ile Leu Ala Asn					
	610		615		620



Tyr Leu Ser Glu Glu Gln Leu Gln Asp Tyr Gln His Phe Val Lys Met  
625 630 635 640

Lys Ser Thr Leu Leu Ile Glu Gln Arg Lys Leu Asp Asp Lys Ile Lys  
645 650 655

Leu Gly Gln Glu Gln Val Lys Cys Leu Leu Glu Ser Leu Pro Ser Asp  
660 665 670

Phe Ile Pro Lys Ala Gly Ala Leu Ala Leu Pro Pro Asn Leu Thr Ser  
675 680 685

Glu Pro Ile Pro Ala Gly Gly Cys Thr Phe Ser Gly Ile Phe Pro Thr  
690 695 700

Leu Thr Ser Pro Leu  
705

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 282 to nucleotide 565;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 342 to nucleotide 565;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AX65\_22 deposited under accession number ATCC 98196;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AX65\_22 deposited under accession number ATCC 98196;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX65\_22 deposited under accession number ATCC 98196;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX65\_22 deposited under accession number ATCC 98196;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

2. A composition of claim 1 wherein said polynucleotide is operably linked to an expression control sequence.

3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.
5. A process for producing a protein, which comprises:
  - (a) growing a culture of the host cell of claim 3 in a suitable culture medium; and
  - (b) purifying the protein from the culture.
6. A protein produced according to the process of claim 5.
7. The protein of claim 6 comprising a mature protein.
8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:
  - (a) the amino acid sequence of SEQ ID NO:2;
  - (b) fragments of the amino acid sequence of SEQ ID NO:2; and
  - (c) the amino acid sequence encoded by the cDNA insert of clone AX65\_22 deposited under accession number ATCC 98196;the protein being substantially free from other mammalian proteins.
9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.
10. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.
11. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 10.
12. The gene corresponding to the cDNA sequence of SEQ ID NO:1 or SEQ ID NO:3.
13. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:56;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:56 from nucleotide 192 to nucleotide 2318;
- (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BD335\_14 deposited under accession number ATCC 98196;
- (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BD335\_14 deposited under accession number ATCC 98196;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BD335\_14 deposited under accession number ATCC 98196;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BD335\_14 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:57;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:57 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

14. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:57;
  - (b) the amino acid sequence of SEQ ID NO:57 from amino acid 148 to amino acid 240;
  - (c) fragments of the amino acid sequence of SEQ ID NO:57; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone BD335\_14 deposited under accession number ATCC 98196;
- the protein being substantially free from other mammalian proteins.

15. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:56.
16. A composition comprising an isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
  - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 206 to nucleotide 391;
  - (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BG241\_1 deposited under accession number ATCC 98196;
  - (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BG241\_1 deposited under accession number ATCC 98196;
  - (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG241\_1 deposited under accession number ATCC 98196;
  - (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG241\_1 deposited under accession number ATCC 98196;
  - (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;
  - (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;
  - (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and
  - (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.
17. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:10;
  - (b) fragments of the amino acid sequence of SEQ ID NO:10; and
  - (c) the amino acid sequence encoded by the cDNA insert of clone BG241\_1 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins.

18. The gene corresponding to the cDNA sequence of SEQ ID NO:9, SEQ ID NO:8 or SEQ ID NO:11.

19. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 194 to nucleotide 328;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BL187\_4 deposited under accession number ATCC 98196;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BL187\_4 deposited under accession number ATCC 98196;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BL187\_4 deposited under accession number ATCC 98196;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BL187\_4 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

20. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:14;
- (b) fragments of the amino acid sequence of SEQ ID NO:14; and

(c) the amino acid sequence encoded by the cDNA insert of clone BL187\_4 deposited under accession number ATCC 98196; the protein being substantially free from other mammalian proteins.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:13, SEQ ID NO:12 or SEQ ID NO:15.

22. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16 from nucleotide 2 to nucleotide 309;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16 from nucleotide 131 to nucleotide 309;
- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BL249\_18 deposited under accession number ATCC 98196;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BL249\_18 deposited under accession number ATCC 98196;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BL249\_18 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BL249\_18 deposited under accession number ATCC 98196;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:17;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:17 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

23. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:17;
- (b) the amino acid sequence of SEQ ID NO:17 from amino acid 2 to amino acid 101;
- (c) fragments of the amino acid sequence of SEQ ID NO:17; and
- (d) the amino acid sequence encoded by the cDNA insert of clone BL249\_18 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins.

24. The gene corresponding to the cDNA sequence of SEQ ID NO:16 or SEQ ID NO:18.

25. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20 from nucleotide 459 to nucleotide 539;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BO71\_1 deposited under accession number ATCC 98196;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BO71\_1 deposited under accession number ATCC 98196;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BO71\_1 deposited under accession number ATCC 98196;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BO71\_1 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:21;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:21 having biological activity;



- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

26. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:21;
- (b) fragments of the amino acid sequence of SEQ ID NO:21; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

BO71\_1 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins.

27. The gene corresponding to the cDNA sequence of SEQ ID NO:20, SEQ ID NO:19 or SEQ ID NO:22.

28. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24 from nucleotide 300 to nucleotide 512;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24 from nucleotide 372 to nucleotide 512;
- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BO365\_2 deposited under accession number ATCC 98196;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BO365\_2 deposited under accession number ATCC 98196;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BO365\_2 deposited under accession number ATCC 98196;

- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BO365\_2 deposited under accession number ATCC 98196;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:25;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:25 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

29. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:25;
- (b) fragments of the amino acid sequence of SEQ ID NO:25; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

BO365\_2 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins.

30. The gene corresponding to the cDNA sequence of SEQ ID NO:24, SEQ ID NO:23 or SEQ ID NO:26.

31. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 68 to nucleotide 328;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BV51\_1 deposited under accession number ATCC 98196;

- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BV51\_1 deposited under accession number ATCC 98196;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV51\_1 deposited under accession number ATCC 98196;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV51\_1 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

32. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:28;
- (b) fragments of the amino acid sequence of SEQ ID NO:28; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

BV51\_1 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins.

33. The gene corresponding to the cDNA sequence of SEQ ID NO:27 or SEQ ID NO:29.

34. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:31;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:31 from nucleotide 57 to nucleotide 396;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BV140\_3 deposited under accession number ATCC 98196;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BV140\_3 deposited under accession number ATCC 98196;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV140\_3 deposited under accession number ATCC 98196;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV140\_3 deposited under accession number ATCC 98196;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:32;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:32 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

35. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:32;

(b) the amino acid sequence of SEQ ID NO:32 from amino acid 29 to amino acid 57;

(c) fragments of the amino acid sequence of SEQ ID NO:32; and

(d) the amino acid sequence encoded by the cDNA insert of clone BV140\_3 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins.

36. The gene corresponding to the cDNA sequence of SEQ ID NO:31, SEQ ID NO:30 or SEQ ID NO:33.

37. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34 from nucleotide 132 to nucleotide 242;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BV141\_2 deposited under accession number ATCC 98196;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BV141\_2 deposited under accession number ATCC 98196;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV141\_2 deposited under accession number ATCC 98196;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV141\_2 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:35;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:35 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

38. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:35;
- (b) fragments of the amino acid sequence of SEQ ID NO:35; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

BV141\_2 deposited under accession number ATCC 98196;

the protein being substantially free from other mammalian proteins.

39. The gene corresponding to the cDNA sequence of SEQ ID NO:34 or SEQ ID NO:36.

40. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:37;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:37 from nucleotide 28 to nucleotide 351;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:37 from nucleotide 328 to nucleotide 351;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone CC194\_4 deposited under accession number ATCC 98196;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone CC194\_4 deposited under accession number ATCC 98196;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CC194\_4 deposited under accession number ATCC 98196;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CC194\_4 deposited under accession number ATCC 98196;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:38;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:38 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

41. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:38;

- (b) the amino acid sequence of SEQ ID NO:38 from amino acid 56 to amino acid 108;
  - (c) fragments of the amino acid sequence of SEQ ID NO:38; and
  - (d) the amino acid sequence encoded by the cDNA insert of clone CC194\_4 deposited under accession number ATCC 98196;
- the protein being substantially free from other mammalian proteins.

42. The gene corresponding to the cDNA sequence of SEQ ID NO:37 or SEQ ID NO:39.

43. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:41;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:41 from nucleotide 62 to nucleotide 592;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone DA136\_11 deposited under accession number ATCC 98196;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone DA136\_11 deposited under accession number ATCC 98196;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DA136\_11 deposited under accession number ATCC 98196;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DA136\_11 deposited under accession number ATCC 98196;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:42;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:42 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

44. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

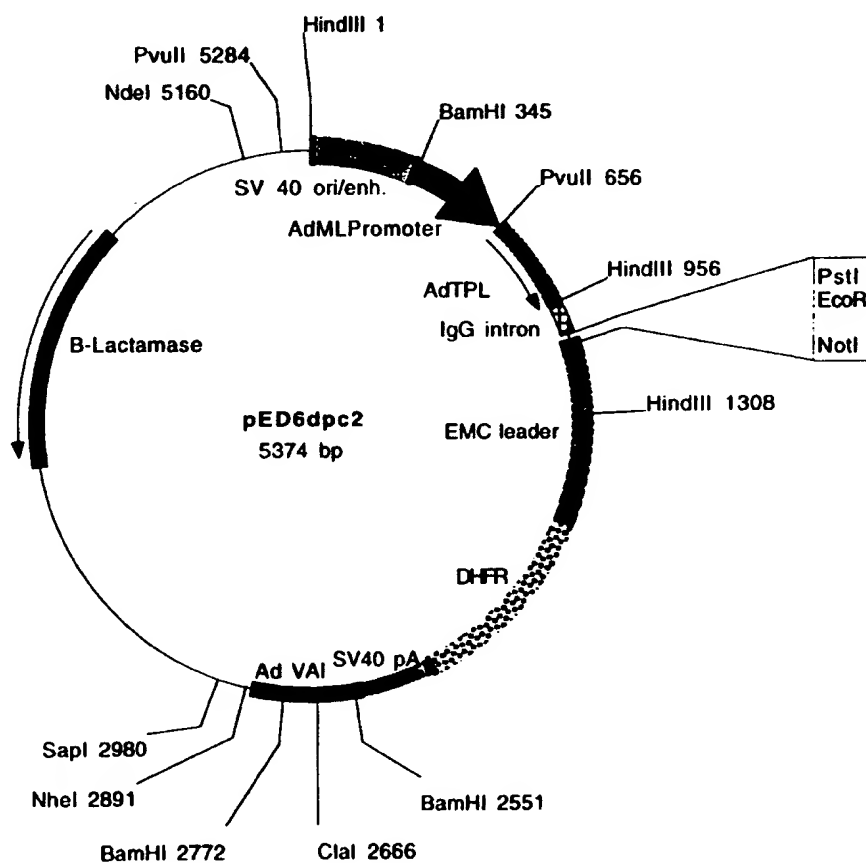
- (a) the amino acid sequence of SEQ ID NO:42;
- (b) the amino acid sequence of SEQ ID NO:42 from amino acid 61 to amino acid 119;
- (c) fragments of the amino acid sequence of SEQ ID NO:42; and
- (d) the amino acid sequence encoded by the cDNA insert of clone

DA136\_11 deposited under accession number ATCC 98196;  
the protein being substantially free from other mammalian proteins.

45. The gene corresponding to the cDNA sequence of SEQ ID NO:41, SEQ ID NO:40 or SEQ ID NO:43.



FIGURE 1A

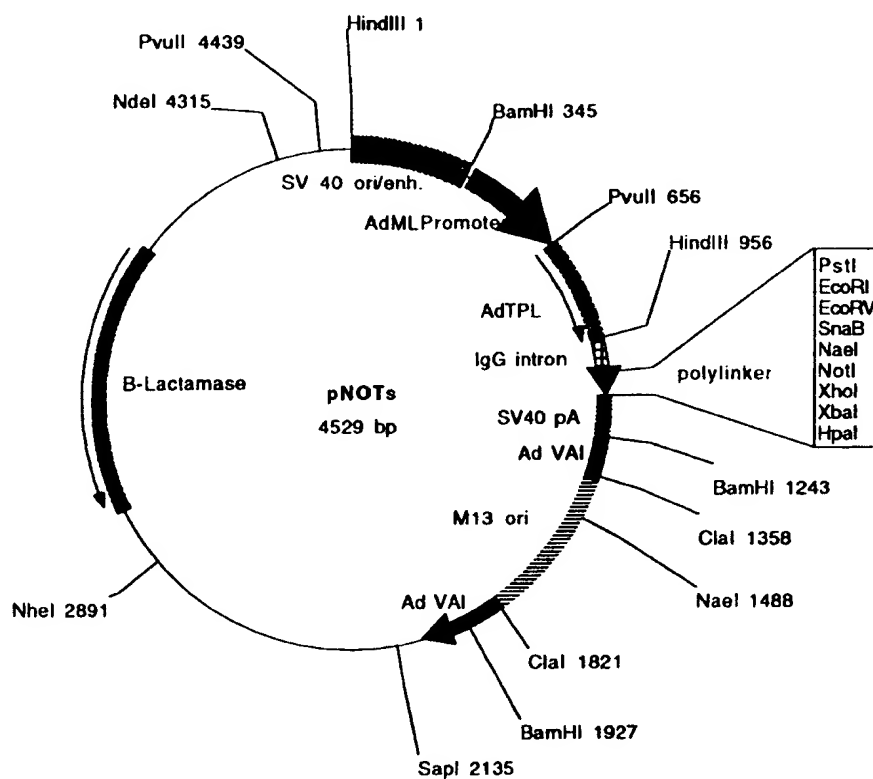


**Plasmid name:** pED6dpc2

**Plasmid size:** 5374 bp

**Comments/References:** pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs

Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI